REMARKS

I. Status of the Claims

Claims 1, 6-13 and 26-30 are pending. Claims 2-5, and 14-25 were previously cancelled. Applicants have also amended claim 6, by deleting "comprising" and inserting "consisting essentially of gelatin, water, sorbitol, sorbitans." Claim 6 has also been amended by inserting "and optionally food coloring and potassium hydroxide." Support for these amendments can be found in the specification on page 15, lines 11-20, and in Table 1 on page 20.. These amendments do not add new matter.

II. The Claims Satisfy the Written Description Requirement

The Office rejects claims 1, 6-13, and 26-30 for allegedly failing to meet the written description requirement of 35 U.S.C. § 112, first paragraph. Office Action, p. 3. According to the Office, "[t]he newly added limitation 'wherein the ibuprofen is not enterically coated' was not literally or implicitly described with reasonable clarity in the claims or any other portion of the originally filed specification." *Id.* at 3-4.

Applicants respectfully traverse. "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." M.P.E.P. § 2163. Applicants submit that the disclosure of the specification demonstrates that Applicants were in possession of the claimed composition because it literally describes a formulation that is not enterically coated. In addition, the nature of the invention inherently supports lack of enteric coating.

Example 2 provides a detailed description of the manufacture of bilayer caplets falling within the scope of the invention. This disclosure does not indicate that the caplet or tablet is enterically coated. Importantly, the specification describes coating of the formulation using Opadry II Blue, followed by dusting with calcium stearate. Specification, p. 23, line 9 to page 24, line 2. No other coating is added. As indicated in the enclosed print-out from the manufacturer of Opadry II Blue (Colorcon), the manufacturer markets several coating formulations, including "Sureteric", for enteric or delayed release formulations. At least Sureteric was available at the time the invention was made. See "Sureteric Aqueous Enteric Coating System", stating "First Published: 02.2000." The instructions for using Sureteric describe first coating the product with Opadry or Opadry II followed by a delayed release coat of Sureteric, and a topcoat of Opadry or Opadry II. Applicants applied Opadry Blue II, but did not apply any additional coating.

Applicants' failure to apply an enteric coating layer, despite the availability of an enteric-coating formulation from the same manufacturer, would convey to the skilled artisan that Applicants were in possession of the explicitly described formulation wherein the caplet or tablet is not enterically coated. The skilled artisan has knowledge of coating systems, including enteric coating layers, and would recognize the significance of not using such a coating in the context of the invention. The nature of the invention would also convey to the skilled artisan that Applicants were in possession of the claimed formulation.

The specification states that "[w]hile not wishing to be bound by theory, the beneficial impact of the combination treatment relies on the rapid impact of ibuprofen due to is pharmacokenetic profile, and continuing effects of both ibuprofen and diphenhydramine." Specification, p. 16, line 20 to page 27, line 3. Enteric coating, which must dissolve before the ibuprofen is released, would delay the onset of ibuprofen's activity. It simply does not make sense that Applicants would first discover a composition that could rapidly induce sleep, and then formulate it in a way that could rob it of its rapid sleep-inducing properties.

Applicants respectfully assert that claims 1, 6-13, and 26-30 satisfy the written description requirement and request that the Office withdraw the rejection.

III. The Bilayer Claims Are Not Anticipated

The Office rejects claims 6-9, and 26 under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,251,426 B1 ("Gullapalli"). Office Action, p. 4. According to the Office, "Gullapalli teaches liquid softgel filled formulations containing ibuprofen in free acid form and softgel capsules comprised of a gelatin sheath comprising ibuprofen and polyethylene glycol." *Id.* at 4-5.

Applicants respectfully traverse. To anticipate, the prior art must literally or inherently disclose all the elements of the claimed invention. See MPEP § 2131. Gullapalli fails to anticipate the claimed invention because it fails to disclose all the elements of the claims. Applicants have amended claim 6 to recite a composition consisting essentially of gelatin, water, sorbitol, and sorbitans, and optionally food

coloring and potassium hydroxide. Gullapalli fails to disclose this formulation and cannot anticipate claim 6, or its dependent claims. Specifically, Gullapalli teaches a formulation containing polyvinylpyrrolidone. The claimed formulation does not contain polyvinylpyrrolidone. Accordingly, Applicants request that the Office withdraw the rejection.

IV. The Claims Are Not Obvious

A. Gullapalli does not render the gel capsule claims obvious

The Office rejects claims 10-13 under 35 U.S.C. § 103(a) as allegedly unpatentable over Gullapalli. Office Action, p. 5. The Office asserts that it would have been obvious to the skilled artisan to used the recited amounts of diphenhydramine in the soft gel capsules taught by Gullapalli. *Id.* at 6.

Applicants respectfully traverse. An obviousness determination requires factual considerations including the scope and content of the prior art, differences between the claimed invention and the prior art, and the level of skill in the art. *See KSR Int'l Co. v. Teleflex Inc.*, 85 U.S.P.Q.2d 1385 (2007); *see also Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The court also noted that "when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." *KSR Int'l*, 85 U.S.P.Q.2d at 1395. Such factors are considered to determine "whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue." *Id.* at 1396.

Gullapalli does not provide any reason why the skilled artisan would arrive at the claimed composition but actually teaches away from it. Gullapalli teaches capsules comprising polyethylene glycol (PEG) **and** polyvinylpyrrolidone (PVP):

> It has been found that these formulations can be prepared by dissolving ibuprofen in a solvent comprised of polyethylene glycol **and** polyvinylpyrrolidone, with each of the solvent components being present in a defined amount in the composition, and with each component having defined characteristics.

Gullapalli, Col. 2, lines 26-31. (emphasis added). Gullapalli explains why a composition comprising both (PEG) and (PVP) was used:

> An additional advantage of these higher amounts of polyvinylpyrrolidone is the apparent reduction in the esterification reaction between the ibuprofen and the polyethylene glycol, a known disadvantage of mixing these two ingredients that results in the reduction of available ibuprofen in its free acid form. Use of the higher percentages of polyvinylpyrrolidone permits a corresponding reduction in the amount of polyethylene glycol required.

Gullapalli, Col. 3, lines 18-25. Thus, Gullapalli discourages a softgel composition comprising PEG and ibuprofen but not PVP. Because claim 6 recites "consisting essentially of", it excludes the presence of PVP, which was recognized by the prior art as a solvent for ibuprofen. Accordingly, Gullapalli provides no reason why the skilled artisan would arrive at a composition consisting essentially of , gelatin, water, sorbitol, sorbitans, ibuprofen and diphenhydramine in amounts effective to treat a pain-associated sleep disturbance, and optionally food coloring and potassium hydroxide, formulated in a soft gelatin capsule containing polyethylene glycol to prevent negative interactions between the ibuprofen and the diphenhydramine.

Applicants respectfully request that the Office withdraw the rejection over Gullapalli.

B. Sunshine and Weng do not render the bilayer claims obvious

The Office rejects claims 1 and 7-13 under 35 U.S.C. 103(a) as allegedly unpatentable over U.S. Patent No. 4,522,826 ("Sunshine") in view of U.S. Patent No. 5,512,300 ("Weng"). Office Action, p. 7. The Office asserts that Sunshine discloses a formulation containing ibuprofen and diphenhydramine which "can be formulated in tablet form or two (bilayer) or more layered tablets." *Id.* at 7. The Office concedes that "Sunshine *et al.* does not teach the separation of ibuprofen and diphenhydramine in different layers." *Id.* However, the Office asserts that "Weng *et al.* report ibuprofen forms low melting point eutectics with diphenhydramine hydrochloride," and concludes that "[i]t would have been obvious to one of ordinary skill in the art to separate diphenhydramine and ibuprofen in different layers" in view of Sunshine and Weng. *Id.* at 8.

Applicants respectfully traverse. A composition comprising ibuprofen and diphenhydramine wherein the ibuprofen and diphenhydramine are separated into different layers and the tablet or caplet is not enterically coated would not arise in the "ordinary course" of research based on the teachings of Sunshine, Weng or their combination because those publications fail to provide any reason why the skilled artisan would arrive at the claimed composition. As stated by the Office, "Sunshine *et*

al. do not teach the separation of ibuprofen and diphenhydramine in different layers." *Id.* at 7. Weng does not provide a reason for separating the actives into two layers.

Weng discusses methods for preparing ibuprofen granulations with improved stability. *See* Abstract and column 3, lines 44-57. *Weng*, however does not solve the problem by physical separation of ibuprofen from another substance but focuses on preparing stabilized ibuprofen through chemical treatment. *Weng* provides no working examples comprising ibuprofen and diphenhydramine or working examples in which ibuprofen and another compound are separated into different layers of a bilayer tablet. Therefore, based on *Weng*, one of ordinary skill in the art might be motivated to use chemically treated ibuprofen in combination with diphenhydramine, but not a bilayer tablet to separate the two. Weng provides no reason why one of skill in the art would have expected a bilayer tablet, in which actives remain in contact at the bilayer interface (because the ibuprofen is not enterically coated), to prevent negative interactions between ibuprofen and diphenhydramine. On the contrary, one of skill in the art would have believed that is was necessary to chemically modify ibuprofen to make such a formulation.

Applicants respectfully request that the Office withdraw the rejection of claims 1 and 7-13 over Sunshine and Weng.

C. Sunshine, Weng, And Drug Facts Do Not Render The Bilayer Claims Obvious

The Office rejects claims 27-30 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sunshine in view of Weng, and further in view of "Drug Facts and

Comparisons" ("Drug Facts"). Office Action, p. 8. The Office relies on its assertions regarding Sunshine and Weng above, but adds that "Sunshine *et al.* teach that 'propionic acid derivatives' including ibuprofen is defined as non-narcotic analgesics/nonsteroidal anti-inflammatory drugs having free -CH(CH3)(COOH)." *Id.* at 9. The Office admits that "Sunshine *et al.* and Weng *et al.* do not teach the onset of action of the composition within 60 minutes," but asserts that Drug Facts teaches that "onset of action of antihistamines including diphenhydramine is within 15 to 30 minutes" and that "onset of ibuprofen is 0.5 hour." *Id.* at 9-10. The Office concludes that the claimed composition would have been obvious because "[i]t is expected that the combination of two agents would possess [the] same onset of action as well-known by the cited reference." *Id.* at 10.

Applicants respectfully traverse. Claims 27-30 recite a formulation in which the ibuprofen is not enterically coated. For the reasons discussed above, these claims are not obvious in view of Sunshine, and Weng. Drug Facts does not concern enteric coating, and thus does not render the claimed formulations obvious.

The publications of record do not render obvious claims 28 and 29, which recite "the ibuprofen is a free acid." It is true that Sunshine defines propionic acids as a class with a free carboxylic acid group; however, Sunshine does not teach that the free acid form occurs in all pharmaceutical formulations. In fact, the remainder of the sentence in which propionic acids are defined states propionic acids "optionally can be in the form of a pharmaceutically acceptable salt group, e.g. --$CH(CH_3)COO^-Na^+$ or --CH_2CH_2 COO^- Na^+). Sunshine, Col. 5, lines 13-19. Thus, Sunshine does not state whether or not a

free acid form of ibuprofen should be used in a particular formulation. And, as Sunshine does not provide any actual examples of tablets, but uses a solution (see Example 1), Sunshine provides no reason why the skilled artisan would choose the free acid form of ibuprofen in the claimed bilayer tablet. In fact, the art of record points in a completely different direction.

The only solution to the negative interaction between ibuprofen and diphenhydramine, prior to the instant invention, is proposed by *Weng*. However, the *Weng* method converts the ibuprofen to a salt. (*See* abstract of Kararli *et al.* "Solid State Interaction of Magnesium Oxide and Ibuprofen to Form a Salt," Pharm. Res. 6: 804-808 (1989)), cited on the face of *Weng*, which teaches that mixing magnesium oxide and ibuprofen results in formation of an ibuprofen-magnesium salt). Moreover, as noted by the instant specification, the acid moiety of ibuprofen may interact with the basic moiety of diphenhydramine. (*See* Specification, page 12, lines 10-12). *Weng* neutralizes the ibuprofen acid, suggesting that the problem of the negative interaction is due to ibuprofen's acid moiety. In addition, interactions between acids and bases are well known in the art. Accordingly, the mere mention of a free acid group in *Sunshine*'s definition of propionic acids would not motivate one of ordinary skill in the art to select the free acid. On the contrary, from the teaching of *Weng*, combined with common knowledge, one of skill in the art would be motivated to avoid the free acid.

Applicants respectfully request that the Office withdraw the rejection.

V. Conclusion

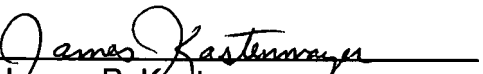
In view of the foregoing, Applicants submit that the pending claims are in condition for allowance. Applicants request reconsideration and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: October 2, 2007

By: 
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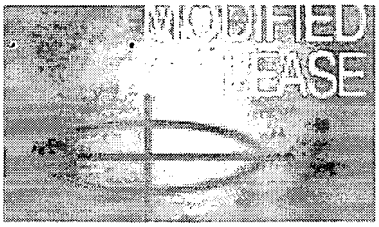
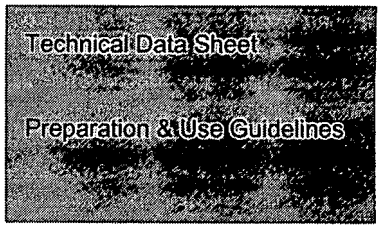


SURETERIC®

AQUEOUS ENTERIC COATING SYSTEM



Sureteric® is a complete aqueous film coating formulation developed to meet the delayed release coating needs of solid oral dosage forms in the pharmaceutical industry. Sureteric is designed for easy preparation, processing and clean up. General use and preparation guidelines are provided in this information sheet

Sureteric Use Guidelines

To ensure enteric protection a three-step coating process is recommended.

1. Subcoat: Opadry® or Opadry II

- Provides a uniform coating surface, reducing the effect of possible substrate imperfections.
- 1 to 2% weight gain of Opadry/Opadry II (formulas Y-1-7000, YS-1-7003, 03K19229 or Y-30-18037) have provided adequate results.

2. Delayed Release Coating: Sureteric

- Sureteric is reconstituted to a 15% solids suspension
- 8 to 10% weight gain is recommended for enteric protection

3. Topcoat: Opadry/Opadry II

- Opadry/Opadry II formulations provide a protective clear gloss or custom color coating
- 0.5 to 1.0% weight gain for a clear coat
- 2 to 3.5% for a custom color coat

Sureteric Preparation Guidelines

Materials

- Sureteric formulated powder
- Cold purified water, maximum temperature 30°C
- Antifoam emulsion - Dow Corning 30% Simethicone USP (7-9245) or equivalent used at 0.33% of Sureteric solids

Equipment

- Variable speed mixer capable of producing and maintaining a vigorous vortex
- High efficiency propeller stirrer with diameter equivalent to 25-30% of the diameter of the mixing vessel
- Mixing vessel to contain a liquid volume 20% greater than the total suspension being prepared. (This is to accommodate the initial foam generated with the addition of the Sureteric powder.)
- 250 micron (60 mesh) sieve

Mixing Procedure

1. Determine the amount of Sureteric, antifoam emulsion (0.33% of Sureteric solids) and water required based on the quantity of tablets to be coated and the target coating weight.

Example *

To coat 10 kg of tablets at a 10% weight gain
1000.0 g Sureteric
5685.6 g water
3.3 g antifoam emulsion

2. Weigh the water into the mixing vessel.
3. Using the propeller stirrer, stir the water to form a vigorous vortex.
4. Weigh the antifoam and add to the water.
5. Weigh the Sureteric and add to the vortex in a slow steady stream while maintaining a vigorous vortex. An increase in volume of the suspension and some foaming will occur initially, but will subside rapidly.
6. Reduce mixer speed to low and continue to mix for 30-45 minutes. The suspension **must** be continuously mixed at low speed throughout the coating process.
7. Pass the suspension through a 250 micron sieve prior to use or use an in-line filter during the coating process.
8. The suspension should be used the same day it is prepared. Colorcon's microbial data shows suspension stability of up to 72 hours.

Colorcon®

Sureteric Clean Up Guidelines

- For best results, Sureteric should be cleaned off equipment shortly after the end of the coating run. If the product is allowed to dry, the residual film can be difficult to remove.
- If cleaned properly, Sureteric residue is easily removed using a mild sodium bicarbonate solution. Sodium Bicarbonate ($NaHCO_3$) is regarded essentially as a non-toxic and non irritating material. It is GRAS listed and has compendial status within the USP, BP, JP, and PhEur.

Cleaning Exposed Surfaces

- Prepare a solution of 10% sodium bicarbonte and water.
- Spray this solution onto the surfaces to be cleaned. Heavier residue areas can be treated directly with the sodium bicarbonate powder.
- Wait 3-5 minutes for the solution to settle on the sprayed surfaces.
- Rinse the sprayed surfaces with deionized water until clean.

Coating Pans

- Coating pans can be cleaned with the same 10% solution of sodium bicarbonate and water.
- Fill the reservoir with the pre-mixed solution and allow the pan to rotate through the solution for 30 minutes.

Spray Equipment

- Spray equipment (guns and hoses) should be disassembled and cleaned.
- When cleaning spray guns, it is important to make sure the passages are free of residual coating material that can block the orifice and restrict flow.
- A thin soft brush or swab can be passed through the tip of the gun to ensure all the coating material is removed. Avoid using hard substances because these can damage the gun parts.

All equipment should be rinsed with deionized water after cleaning

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